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Clinical paper

Neuron-specific enolase (NSE) improves clinical risk scores for prediction of neurological outcome and death in cardiac arrest patients: Results from a prospective trial

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Abstract

Aim: Neuron-specific enolase (NSE) increases in response to brain injury and is recommended for outcome prediction in cardiac arrest patients. Our aim was to investigate whether NSE measured at different days after a cardiac arrest and its kinetics would improve the prognostic ability of two cardiac arrest specific risk scores.

Methods: Within this prospective observational study, we included consecutive adult patients after cardiac arrest. We calculated the Out-of-hospital cardiac arrest (OHCA) score and the Cardiac Arrest Hospital Prognosis (CAHP) score upon ICU admission and measured serum NSE upon admission and days 1, 2, 3, 5 and 7. We calculated logistic regression models to study associations of scores and NSE levels with neurological outcome defined by Cerebral Performance Category (CPC) scale and in-hospital death.

Results: From 336 included patients, 180 (54%) survived until hospital discharge, of which 150 (45%) had a good neurological outcome. NSE at day 3 showed the highest prognostic accuracy (discrimination) for neurological outcome (area under the curve (AUC) 0.89) and in-hospital mortality (AUC 0.88). These results were robust in reclassification statistics and across different subgroups. NSE kinetics with admission levels serving as a baseline did not further improve prognostication. NSE on day 3 significantly improved discrimination of both clinical risk scores (CAHP from AUC 0.81 to 0.91; OHCA from AUC 0.79 to 0.89).

Conclusion: NSE measured at day 3 significantly improves clinical risk scores for outcome prediction in cardiac arrest patients and may thus add to clinical decision making about escalation or withdrawal of therapy in this vulnerable patient population.

Keywords: Neuron-specific enolase, Cardiac arrest, Cardiopulmonary resuscitation, Prognosis

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Introduction

Patients resuscitated from cardiac arrest are at high risk for in-hospital mortality or discharge with permanent brain injury and functional disability.[1–3] Risk stratification in the early course of post-cardiac arrest care is important because it influences therapeutic decisions regarding possible withdrawal of therapy.[3] Having a real understanding of potentially prognostic information and their context can lead, in conjunction with knowledge of the patients' presumed will, to the most rational decision making discussions.

Several studies have investigated predictors of neurological outcome and mortality after cardiopulmonary resuscitation (CPR).[4,5] Among laboratory parameters, the neuron-specific enolase (NSE) has been investigated in several studies for its prognostic ability.[6–8] Enolase γ is an enzyme located mainly within neurons and neuroectodermal cells, and converts anaerobically glucose to metabolites suitable for oxidation.[9,10] In healthy individuals, serum NSE levels remain low.[11] After neuronal tissue damage such as brain injury or stroke, however, NSE levels in the blood show a strong increase and thus act as a biomarker for brain damage.[9]

Based on several clinical studies, the American Academy of Neurology (AAN) in 2006 recommended that a NSE level above 33 ng/mL during days 1 through 3 was an indicator for an unfavorable prognosis.[4] More recent work, however, has challenged these recommendations and indicated that the accuracy of serum-NSE may be lower than anticipated due to several reasons including therapeutic hypothermia.[6,12–14] As a consequence, the 2015 European Resuscitation Council Guidelines for Resuscitation still recommend to measure NSE levels 48–72 h after cardiac arrest, but also point to the lower accuracy of NSE compared to more specific neurological examinations including pupillary reflexes and somatosensory evoked potential (SSEP).[1]

Recently, two cardiac arrest specific clinical risk scores including the Out-of-hospital cardiac arrest (OHCA) score and Cardiac Arrest Hospital Prognosis (CAHP) score have been proposed to improve the prognostic assessment of patients.[15–17] Our aim was to investigate whether NSE measured at different days after a cardiac arrest and its kinetics would improve the prognostic ability of the CAHP and the OHCA scores to predict neurological outcome and in-hospital death.

Methods

Study setting

For this prospective, observational study (COMMUNICATE), we included patients from October 2012 until August 2017 at University Hospital of Basel, Switzerland. COMMUNICATE assessed in parallel data from patients suffering from a cardiac arrest and their relatives.[17–19] The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Northwest and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ). Patients had to sign a consent form to be included in the study. In case they were unable to sign the form themselves due to unconsciousness after cardiac arrest, a relative of the patient could sign it in accordance with the presumed will of the patient. If no next-of-kin was readily available, a physician in the treatment team, who was not involved in the study, was asked to confirm that there were no medical grounds hindering participation in the study. In these cases, the patient or next-of-kin were asked to confirm the inclusion at a later point in time.

Study population and treatment of patients during the trial

Consecutive adult patients (≥16 years) who experienced a cardiac arrest and who were admitted to the intensive care unit (ICU) at University Hospital of Basel were eligible. Patients were excluded in case of monitored in-hospital cardiac arrest (IHCA) or if all NSE data points were missing.

The treatment of patients regarding the cardiac arrest was based on the clinical routine in our intensive care unit without interaction with the research team. In 2012, all consecutive patients without complete recovery to premorbid neurofunctional baseline within the first hour following resuscitation were treated with in-hospital systemic cooling via the thermogard XP temperature management system (ZOLL® Medical Corporation, Chelmsford, MA, USA) as a neuroprotectant measure to a target core temperature of 93.2 °F (i.e., 34.0 °C) for 24 h followed by a rewarming phase with a controlled increase of the core temperature (i.e., 0.2 °F or 0.1 °C) per hour until 99.5 °F (i.e., 37.5 °C). Since 2013 (following the TTM-trial[20]), all consecutive patients without complete recovery were cooled to a target core temperature of 96.8 °F (i.e., 36.0 °C) for 28 h followed by the rewarming phase using the same thermogard XP temperature management system as mentioned above. Patients with core temperatures below the target temperature were rewarmed with 32.9 °F (i.e., 0.5 °C) to meet the target core temperatures.

We also routine conducted clinical, laboratory and neurophysiologic assessments for the purpose of prognostication of presumed outcome 72 h after CPR and complete rewarming according to guidelines and other recommendations.[4,5,21] In short, full clinical neurologic examination was followed by a spot electroencephalography (EEG) recorded for at least 20 min in patients without complete recovery to their premorbid neurofunctional baseline. These tests were complemented by somatosensory evoked potentials (SSEPs), biochemical markers of brain injury (e.g., NSE), and neuroimaging with magnetic resonance imaging studies.

Based upon the degree of clinical recovery and predictive data from the prognostic tests mentioned, withdrawal of life-sustaining therapy was done after in-depth discussion within the treating team and the patients' family based on presumed patients' will, the medical and social situation and the patients prognosis as assessed by all available clinical, neurological and laboratory data (including levels of NSE). Again, there was no influence of the study team on these decisions.

Data collection

Blood samples for measurement of NSE levels were drawn at ICU admission (day 0) and on days 1, 2, 3, 5 and 7 using an Electro-Chemi-Luminescent-Immuno-Assay (ECLIA) kit (Roche Diagnostics, Rotkreuz, Switzerland). In addition, we collected other routine blood markers including pH, lactate and creatinine. Resuscitation information (i.e., no-flow time (time from cardiac arrest to start of

basic life support (BLS)), low-flow time (time from start of BLS to return of spontaneous circulation (ROSC)), cardiac arrest setting, bystander observing the cardiac arrest and providing CPR, initial rhythm, epinephrine dose given during resuscitation), as well as socio-demographics (i.e., age, gender) and comorbidities (i.e., coronary disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease (COPD), malignant disease, diabetes, renal failure, liver failure, neurological disease) were prospectively collected by trained research coordinators using a structured data collection form. We did not collect data regarding neurological exams.

The Out-of-hospital cardiac arrest (OHCA) score and Cardiac Arrest Hospital Prognosis (CAHP) score were calculated as recommended in the original publications.[15,16] The treating physician team was blinded to the results of these risk scores as they are not in common use in the ICU and were calculated during data collection and analysis and therefore exclusively part of study data.

Outcomes

The primary endpoint was neurological outcome at hospital discharge defined by the Cerebral Performance Category (CPC) scale. CPC was prospectively assessed by a trained study nurse at discharge. According to previous studies, no neurological deficit (CPC = 1) and moderate disability (CPC = 2) were considered good neurological outcomes. Severe disability (CPC = 3), coma or vegetative state (CPC = 4) and death (CPC = 5) were defined as bad neurological outcome.[22,23] Secondary endpoint was in-hospital mortality (CPC = 5).

Statistical analysis

The patient cohort was characterized by descriptive statistics such as means, medians and inter-quartile ranges for continuous variables and frequencies for binary or categorical variables. Receiver operating characteristics (ROC) and corresponding

Table 1 – Baseline characteristics.

	All	CPC 1–2	CPC 3–5	p-Value
N	336	150	186	
Sociodemographics				
Age, years, mean (SD)	64 (14.4)	61 (14.8)	66 (13.6)	0.001
Male gender	243 (72.3%)	124 (82.7%)	119 (64.0%)	<0.001
Comorbidities				
Coronary artery disease	218 (64.9%)	116 (77.3%)	102 (54.8%)	<0.001
Congestive heart failure	59 (17.6%)	24 (16.0%)	35 (18.8%)	0.50
COPD	30 (8.9%)	9 (6.0%)	21 (11.3%)	0.091
End-stage liver disease	5 (1.5%)	1 (0.7%)	4 (2.2%)	0.26
Hypertension	174 (51.8%)	82 (54.7%)	92 (49.5%)	0.34
Diabetes	82 (24.4%)	30 (20.0%)	52 (28.0%)	0.091
Renal failure	52 (15.5%)	22 (14.7%)	30 (16.1%)	0.71
Malignant disease	40 (11.9%)	10 (6.7%)	30 (16.1%)	0.008
Neurological disease	32 (9.5%)	9 (6.0%)	23 (12.4%)	0.048
Resuscitation information				
No-flow time, min, mean (SD)	4.1 (6.1)	1.8 (3.4)	6.1 (7.1)	<0.001
Low-flow time, min, mean (SD)	19.3 (15.4)	15.1 (12.2)	22.7 (16.9)	<0.001
Witnessed cardiac arrest	278 (83.0%)	139 (92.7%)	139 (75.1%)	<0.001
Bystander CPR	209 (62.4%)	111 (74.0%)	98 (53.0%)	<0.001
Arrest setting				
At home	124 (37.0%)	33 (22.1%)	91 (48.9%)	<0.001
In public	157 (46.9%)	89 (59.7%)	68 (36.6%)	
In-hospital (not monitored)	54 (16.1%)	27 (18.1%)	27 (14.5%)	
Initial heart rhythm				
Ventricular tachycardia	18 (5.4%)	11 (7.3%)	7 (3.8%)	<0.001
Ventricular fibrillation	170 (50.7%)	103 (68.7%)	67 (36.2%)	
Asystole	61 (18.2%)	6 (4.0%)	55 (29.7%)	
Pulsless electrical activity	74 (22.1%)	22 (14.7%)	52 (28.1%)	
Unknown	12 (3.6%)	8 (5.3%)	4 (2.2%)	
Cause of cardiac arrest				
Coronary artery disease	164 (48.8%)	88 (58.7%)	76 (40.9%)	0.001
Primary arrhythmia	70 (20.8%)	35 (23.3%)	35 (18.8%)	0.31
Respiratory reason	60 (17.9%)	19 (12.7%)	41 (22.0%)	0.026

Data presented as n (%) or mean (SD). COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation. CPC, cerebral performance category.

Table 2.1 – Comparison between NSE levels on different days to predict neurological outcome.

	N	All	CPC 1–2	CPC 3–5	p-Value	Standardized OR per decile	Standardized OR per decile adjusted	ROC AUC
N		336	150	186				
NSE day 0	273	34.2 (24.4, 51.4)	28 (21, 41.3)	39.1 (29.2, 77.5)	<0.001	1.26 (1.15–1.38), p < 0.001	1.36 (1.22–1.53), p < 0.001	0.68 (0.62–0.74)
NSE day 1	285	34.8 (24.4, 68.2)	27.5 (19, 37)	52.4 (31.2, 111.9)	<0.001	1.48 (1.34–1.64), p < 0.001	1.63 (1.44–1.85), p < 0.001	0.77 (0.72–0.83)
NSE day 2	241	30.7 (19.8, 104.1)	22.3 (16.9, 28.5)	98.7 (37.6, 220.5)	<0.001	1.94 (1.66–2.27), p < 0.001	2.26 (1.84–2.77), p < 0.001	0.88 (0.84–0.93)
NSE day 3	187	29.5 (17.6, 117.8)	19 (14.5, 26.3)	109.9 (39.45, 215.15)	<0.001	2.01 (1.67–2.42), p < 0.001	2.35 (1.83–3.01), p < 0.001	0.89 (0.84–0.93)
NSE day 5	102	21.85 (16.1, 44.6)	17.3 (13.9, 22.3)	44.6 (27.4, 84.2)	<0.001	1.68 (1.37–2.05), p < 0.001	1.81 (1.4–2.33), p < 0.001	0.83 (0.75–0.92)
NSE day 7	56	19.35 (15.4, 28.9)	17.4 (14.3, 22.9)	26.2 (17.2, 38.5)	0.006	1.34 (1.08–1.66), p = 0.007	1.47 (1.05–2.07), p = 0.026	0.71 (0.58–0.85)
ΔNSE day 0–1	230	1.8 (−4.7, 20.8)	−2.3 (−6.1, 2)	14.45 (0.6, 35.45)	<0.001	1.46 (1.3–1.63), p < 0.001	1.45 (1.28–1.64), p < 0.001	0.77 (0.71–0.83)
ΔNSE day 0–2	185	0.1 (−10.3, 57.5)	−7.4 (−15.9, −0.9)	57.85 (7.4, 174.2)	<0.001	1.85 (1.56–2.19), p < 0.001	1.85 (1.54–2.22), p < 0.001	0.86 (0.80–0.92)
ΔNSE day 0–3	141	−2.3 (−13.5, 57.5)	−11.45 (−21.7, −2.3)	58.6 (3.3, 182.1)	<0.001	1.9 (1.56–2.32), p < 0.001	2.05 (1.61–2.60), p < 0.001	0.87 (0.81–0.93)
ΔNSE day 0–5	82	−8.75 (−22.2, 6.9)	−14.95 (−30.55, −5.3)	9.45 (−10.1, 54.1)	<0.001	1.49 (1.22–1.82), p < 0.001	1.47 (1.17–1.86), p=0.001	0.78 (0.67–0.89)
ΔNSE day 0– 7	44	−14 (−27.75, −5.9)	−16.2 (−32.1,−6.8)	−11.1 (−16.8, −5)	0.27	1.11 (0.9–1.38), p = 0.333	1.12 (0.74–1.7), p = 0.586	0.60 (0.43–0.77)

Data presented as median (interquartile range) or mean (95% confidence interval). NSE, neuron specific enolase; Δ, delta, difference; CPC, cerebral performance category; OR, odds ratio; ROC, receiver operating characteristics curve; AUC, area under the curve.

areas under the curve (AUC) were calculated to evaluate the discrimination of NSE.

We used univariate and multivariate logistic regression analysis with calculation of odds ratios (OR) and 95% confidence intervals (CI) to determine associations between NSE, sociodemographic and clinical variables and neurological outcome. NSE levels were divided into deciles for standardization of ORs and better comparability. For each sampling day, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated as percentages with 95% CI, as were positive and negative likelihood ratios. Optimal cutoff levels of NSE at the different time points for our patient cohort were estimated according to Youden index. OHCA and CAHP score risk categories were calculated using cutoffs as proposed in previous publications.[15,16] To understand whether NSE would improve the prognostic ability of the two risk scores, we calculated nested bivariate models using risk score ±NSE values at the different time points and compared the result to the risk score alone in terms of AUC results. We also calculated the Net Reclassification Index (NRI) across risk categories of 5%, 10%, 30%, 50% and 80% and the Integrated Discrimination Index (IDI) as proposed by Pencina et al.[24]

Finally, we performed predefined subgroup analysis to understand whether differences in prognostic performance exist within certain patient groups based on gender, age, circumstances of resuscitation (i.e., bystander starting CPR, initial shockable rhythm, epinephrine dose given during resuscitation), temperature management (hypothermia (TMH) and targeted management (TTM)) and use of an impella device. A p-value <0.05 was considered statistically significant and all statistical analyses were performed using STATA 12.0.

Results

Baseline characteristics

Between October 2012 and August 2017, 390 patients were admitted to the ICU of the University Hospital of Basel after successful resuscitation from a cardiac arrest. Out of 390, 336 (86%) patients were included in this study. Reasons for non-inclusion were lack of informed consent (n = 37), monitored in-hospital cardiac arrest (n = 4) or missing of all NSE data points (n = 13). All patients had at least 1 NSE measurement, and we had NSE results on admission in 274 patients, on day 1 on 285 patients, on day 2 on 241 patients, on the 3 of 187 patients and on day 5 on 102 patients.

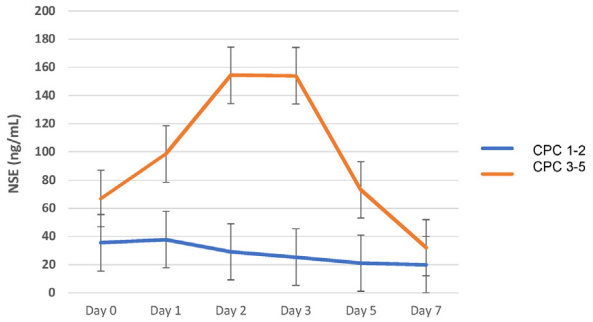

Fig. 1 – Line plot, NSE (neuron specific enolase) levels associated with neurological outcome; CPC, cerebral performance category.

Table 2.2 – Comparison between NSE levels on different days to predict in-hospital death.

	N	All	Survivors	In-hospital deaths	p-Value	Standardized OR per decile	Standardized OR per decile adjusted	ROC AUC
N		336	180	156				
NSE day 0	273	34.2 (24.4, 51.4)	29.8 (21.4, 40.8)	40.6 (29.8, 83.2)	<0.001	1.31 (1.19–1.44), p < 0.001	1.38 (1.23–1.54), p < 0.001	0.7 (0.64–0.77)
NSE day 1	285	34.8 (24.4, 68.2)	28.1 (20.7, 39.6)	59.2 (33.5, 120)	<0.001	1.44 (1.3–1.6), p < 0.001	1.56 (1.38–1.76), p < 0.001	0.76 (0.70–0.82)
NSE day 2	241	30.7 (19.8, 104.1)	23.3 (17.3, 32.1)	118.7 (43.1, 257.1)	<0.001	1.86 (1.59–2.16), p < 0.001	1.97 (1.65–2.35), p < 0.001	0.87 (0.82–0.92)
NSE day 3	187	29.5 (17.6, 117.8)	20.7 (16, 34)	134 (49.9, 281.9)	<0.001	1.97 (1.63–2.37), p < 0.001	2.18 (1.73–2.75), p < 0.001	0.88 (0.83–0.94)
NSE day 5	102	21.85 (16.1, 44.6)	17.8 (14.1, 25.6)	68.4 (30.6, 98)	<0.001	1.85 (1.44–2.39), p < 0.001	2.24 (1.51–3.33), p < 0.001	0.86 (0.79–0.94)
NSE day 7	56	19.35 (15.4, 28.9)	18.8 (14.9, 26.1)	26.2 (16.7, 47.9)	0.063	1.21 (0.97–1.51), p = 0.089	1.19 (0.83–1.71), p = 0.334	0.66 (0.49–0.84)
ΔNSE day 0–1	230	1.8 (−4.7, 20.8)	−1.3 (−5.9, 2.9)	16.8 (1.7, 37.2)	<0.001	1.44 (1.29–1.61), p < 0.001	1.46 (1.29–1.66), p < 0.001	0.77 (0.70–0.83)
ΔNSE day 0–2	185	0.1 (−10.3, 57.5)	−6.4 (−13.6, 0.5)	72.5 (14.25, 186.85)	<0.001	1.88 (1.57–2.24), p < 0.001	1.89 (1.56–2.3), p < 0.001	0.86 (0.80–0.93)
ΔNSE day 0–3	141	−2.3 (−13.5, 57.5)	−8.7 (−20.7, −1.7)	93.8 (10.1, 215.5)	<0.001	1.94 (1.57–2.39), p < 0.001	2.07 (1.63–2.64), p < 0.001	0.88 (0.81–0.94)
ΔNSE day 0–5	82	−8.75 (−22.2, 6.9)	−13.35 (−24.5, −4.2)	19.9 (−5.85, 71.55)	<0.001	1.55 (1.24–1.94), p < 0.001	1.57 (1.2–2.06), p = 0.001	0.80 (0.67–0.93)
ΔNSE day 0–7	44	−14 (−27.75, −5.9)	−13.55 (−29.15, −6.85)	−14 (−24.5, −2.5)	0.60	1.06 (0.84–1.34), p = 0.63	1.1 (0.66–1.82), p = 0.719	0.55 (0.35–0.75)

Data presented as median (interquartile range) or mean (95% confidence interval). NSE, neuron specific enolase; Δ, delta, difference; OR, odds ratio; ROC, receiver operating characteristics curve; AUC, area under the curve.

From 336 included patients, 180 (54%) survived until hospital discharge and thereof 150 (45%) had a good neurological outcome. Table 1 shows baseline characteristics stratified by neurological outcome. Mean age of the cohort was 64 years and 72.3% were males. Most patients had OHCA, but in 16.1% (n = 54) the cardiac arrest was in-hospital (not monitored). There were significant differences in regard to age, gender and comorbidities among the two groups. Participants with poor neurological outcome were older, more often female and had higher prevalence of malignant or neurological disease.

Association between NSE blood levels and primary and secondary outcomes

First, NSE blood levels were compared at ICU admission and on days 1, 2, 3, 5 and 7 between patients with good or bad neurological outcome (Table 2.1). NSE levels in patients with bad outcome were higher on each day with the biggest difference on day 3 as depicted in Fig. 1. This was confirmed in an univariate and multivariate logistic regression analysis adjusted for age, gender and comorbidities (i.e., coronary artery disease, congestive heart failure, COPD, end stage liver failure, chronical renal failure, malignant disease, neurological disease, hypertension, diabetes). Again, NSE levels on day 3 showed the strongest association with neurological outcome (adjusted OR per decile 2.35 (95% CI 1.83–3.01), $p < 0.001$); AUC of 0.89).

Results were similar for the endpoint in-hospital mortality (Table 2.2), with again NSE levels on day 3 showing the strongest association with outcome (adjusted OR per decile 2.18 (95% CI 1.73–2.75, $p < 0.001$); AUC of 0.88).

Further we calculated sensitivity and specificity, positive and negative predictive value as well as positive and negative likelihood ratios for NSE at the formerly recommended cut-off (33 ng/mL), as well as for the optimal cutoff based on ROC analysis (Tables 3.1 and 3.2). On day 3, sensitivity and specificity were 79.3% and 82.1%, with 81.1% positive predictive value and 80.4% negative predictive value. The calculated optimal cutoffs for day 3 was at a threshold of 41.8 ng/mL with a corresponding sensitivity of 73.9% and a specificity of 89.5% for poor neurological outcome.

Association between NSE kinetics and outcome

In a second step, we calculated NSE kinetics (i.e., the mean magnitude of increase from baseline to each day) (Tables 2.1 and 2.2). Again, the best prognostic performance was found for the difference of NSE between day 0 to day 3 (AUC: 0.87 for neurological outcome and 0.88 for in-hospital mortality). Kinetics were not superior to absolute values for any of the days studied.

Association between NSE blood levels and CAHP and OHCA score

In a next step, we investigated whether NSE would improve established cardiac arrest specific risk scores such as CAHP and OHCA by combining both in a joint logistic regression model (Fig. 2 (2.1) and (2.2)). Day 3 NSE values significantly improved the CAHP score from an AUC of 0.81 to 0.91 ($p < 0.05$). Similarly, NSE improved the OHCA score from an AUC of 0.79 to 0.89 ($p < 0.05$).

Table 3.1 – Performance of NSE at different cutoff points to predict neurological outcome.

	CPC 1–2 below cutoff	CPC 1–2 above cutoff	CPC 3–5 below cutoff	CPC 3–5 above cutoff	Sensitivity	Specificity	PPV	NPV	LLR+	LLR−
Day 0 NSE 33* ng/mL	71	47	55	100	63.9 (55.8–71.4)	60.2 (50.7–69.1)	67.8 (59.6–75.3)	55.9 (46.8–64.7)	1.6 (1.25–2.06)	0.6 (0.46–0.78)
Day 0 NSE 28.1 ng/mL	59	59	33	122	78.2 (70.9–84.4)	50 (40.7–59.3)	67.4 (60.1–74.2)	63.4 (52.8–73.2)	1.56 (1.28–1.91)	0.44 (0.31–0.62)
Day 1 NSE 33* ng/mL	94	44	41	106	72.1 (64.1–79.2)	68.1 (59.6–75.8)	70.7 (62.7–77.8)	69.6 (61.1–77.2)	2.26 (1.74–2.94)	0.41 (0.31–0.54)
Day 1 NSE 40.3 ng/mL	112	26	53	94	63.3 (54.9–71.1)	81.2 (73.6–87.3)	78.2 (69.6–85.2)	67.5 (59.8–74.5)	3.36 (2.33–4.85)	0.45 (0.36–0.57)
Day 2 NSE 33* ng/mL	107	20	24	90	78.9 (70.3–86)	84.3 (76.7–90.1)	81.8 (73.3–88.5)	81.7 (74–87.9)	5.01 (3.32–7.58)	0.25 (0.17–0.36)
Day 2 NSE 34.9 ng/mL	110	17	25	89	77.2 (68.4–84.5)	86.6 (79.4–92)	83.8 (75.3–90.3)	80.9 (73.3–87.1)	5.77 (3.66–9.08)	0.26 (0.19–0.37)
Day 3 NSE 33* ng/mL	78	17	19	73	79.3 (69.6–87.1)	82.1 (72.9–89.2)	81.1 (71.5–88.6)	80.4 (71.1–87.8)	4.43 (2.85–6.91)	0.25 (0.17–0.38)
Day 3 NSE 41.8 ng/mL	85	10	23	69	73.9 (63.7–82.5)	89.5 (81.5–94.8)	87.2 (77.7–93.7)	78 (69–85.4)	7.02 (3.86–12.78)	0.29 (0.21–0.41)
Day 5 NSE 33* ng/mL	52	5	18	27	60 (44.3–74.3)	91.2 (80.7–97.1)	84.4 (67.2–94.7)	74.3 (62.4–84)	6.84 (2.86–16.33)	0.44 (0.3–0.63)
Day 5 NSE 27.4 ng/mL	49	8	11	34	73.3 (58.1–85.4)	86 (74.2–93.7)	80.5 (65.1–91.2)	80.3 (68.2–89.4)	5.22 (2.68–10.17)	0.31 (0.19–0.51)
Day 7 NSE 33* ng/mL	30	1	15	10	40 (21.1–61.3)	96.8 (83.3–99.9)	90.9 (58.7–99.8)	66.7 (51–80)	12.4 (1.7–90.44)	0.62 (0.45–0.86)

Data presented as mean (95% confidence interval). NSE, neuron specific enolase; CPC, cerebral performance category; PPV, positive predictive value; NPV, negative predictive value; LLR+, positive likelihood ratio; LLR−, negative likelihood ratio.
* Youden index: cutoff also at 33 ng/mL.

NSE also showed a significant improvement in regard to the Net Reclassification Index (NRI) of 0.64 ($p < 0.001$) for OHCA (among patients with poor outcome, adding NSE increased the risk in the statistical model in 44%, while decreasing the risk in 17%; and among patients with favorable outcome, adding NSE decreased the risk of the model in 52% while increasing it in 15%). For the CAHP score, there was also a strong improvement with an NRI of 0.75 ($p < 0.001$) (among patients with poor outcome, adding NSE increased the risk in the statistical model in 47%, while decreasing the risk in 17%; and among patients with favorable outcome, adding NSE decreased the risk of the model in 59% while increasing it in 14%. The IDI for OHCA were 0.18 ($p < 0.001$) and for CAHP 0.25 ($p < 0.001$).

Subgroup analysis for primary and secondary endpoint

Finally, we performed subgroup analysis to study differences in performance of NSE of day 3 in specific patient groups in regard to neurological outcome (Fig. 3 (3.1)) and in-hospital mortality (Fig. 3 (3.2)). Higher AUCs were found in younger patients (<55 years), females and in patients with hypothermia (TMH) and targeted management (TTM) treatment. In patients with an impella device, NSE was inferior in regard to the AUC compared to patients with no impella. We also did the same subgroup analysis for NSE measured at other time points (i.e., days 0, 1 and 2) for both endpoints, neurological outcome (Additional file 1 in Supplementary material) and in-hospital mortality with found similar results (Additional file 2 in Supplementary material).

Discussion

Within this relatively large, prospective cohort of cardiac arrest patients, we found NSE on day 3 to be a reliable and accurate predictor for neurological outcome and in-hospital death. Day 3 measurements were superior to measurements at other days and kinetics based on baseline levels did not further improve prognostication. Also, the results were robust in subgroup analyses with best performance in younger patients and patients with hypo-/isothermia treatment. Importantly, our analysis indicate that adding NSE at day 3 to established clinical risk scores such as OHCA and CAHP further improved discrimination.

Our results are in line with previous studies showing best performance of NSE on days 3 or 4 after cardiac arrest, but lower reliability when measured at earlier time points.[23,25,26] Arguably, the earlier prognostic information is available, the more potential effect on clinical decision making. Herein, the two clinical risk scores (OHCA and CAHP) are based on admission information

Table 3.2 – Performance of NSE at different cutoff points to predict in-hospital death.

	Survivors below cutoff	Survivors above cutoff	In-hospital death below cutoff	In-hospital death above cutoff	Sensitivity	Specificity	PPV	NPV	LLR+	LLR−
Day 0 NSE 33 ng/mL	83	56	43	91	67.2 (58.5–75)	59.7 (51.1–67.9)	61.6 (53.2–69.6)	65.4 (56.4–73.6)	1.67 (1.32–2.11)	0.55 (0.42–0.73)
Day 0 NSE 49.6 ng/mL	123	16	79	55	40 (31.7–48.8)	88.5 (82–93.3)	77.1 (65.6–86.3)	60.3 (53.2–67.1)	3.48 (2.1–5.76)	0.68 (0.58–0.79)
Day 1 NSE 33 ng/mL	107	59	28	91	76.5 (67.8–83.8)	64.5 (56.7–71.7)	60.7 (52.4–68.5)	79.3 (71.4–85.8)	2.15 (1.71–2.70)	0.37 (0.26–0.51)
Day 1 NSE 43.2 ng/mL	131	35	39	80	65.5 (56.3–74)	78.9 (71.9–84.9)	69 (59.6–77.4)	76.2 (69.1–82.3)	3.11 (2.25–4.29)	0.44 (0.34–0.57)
Day 2 NSE 33 ng/mL	116	34	15	76	83.5 (74.3–90.5)	77.3 (69.8–83.8)	69.1 (59.6–77.6)	88.5 (81.8–93.4)	3.68 (2.70–5.02)	0.21 (0.13–0.34)
Day 2 NSE 34.9 ng/mL	119	31	16	75	81.3 (71.8–88.7)	79.3 (72–85.5)	70.5 (60.8–79)	87.5 (80.7–92.5)	3.93 (2.83–5.47)	0.24 (0.15–0.36)
Day 3 NSE 33 ng/mL	85	32	12	58	82.9 (72–90.8)	72.6 (63.6–80.5)	64.4 (53.7–74.3)	87.6 (79.4–93.4)	3.03 (2.21–4.15)	0.24 (0.14–0.40)
Day 3 NSE 47.8 ng/mL	99	18	14	56	78.6 (67.1–87.5)	84.6 (76.8–90.6)	75.3 (63.9–84.7)	86.8 (79.2–92.4)	5.11 (3.28–7.95)	0.25 (0.16–0.4)
Day 5 NSE 33 ng/mL	61	12	9	20	69 (49.2–84.7)	83.6 (73–91.2)	62.5 (43.7–78.9)	87.1 (77–93.9)	4.20 (2.37–7.43)	0.37 (0.21–0.65)
Day 5 NSE 27.4 ng/mL	56	17	4	25	82.8 (64.2–94.2)	76.7 (65.4–85.8)	58.5 (42.1–73.7)	91.8 (81.9–97.3)	3.55 (2.27–5.56)	0.22 (0.1–0.5)
Day 7 NSE 33 ng/mL	36	5	9	6	40 (16.3–67.7)	87.8 (73.8–95.9)	54.5 (23.4–83.3)	80 (65.4–90.4)	3.28 (1.17–9.18)	0.68 (0.45–1.05)
Day 7 NSE 38.5 ng/mL	39	2	9	6	33.3 (11.8–61.6)	95.1 (83.5–99.4)	71.4 (29–96.3)	79.6 (65.7–89.8)	6.83 (1.48–31.54)	0.7 (0.49–1.01)

Data presented as mean (95% confidence interval). NSE, neuron specific enolase; PPV, positive predictive value; NPV, negative predictive value; LLR+, positive likelihood ratio; LLR−, negative likelihood ratio.

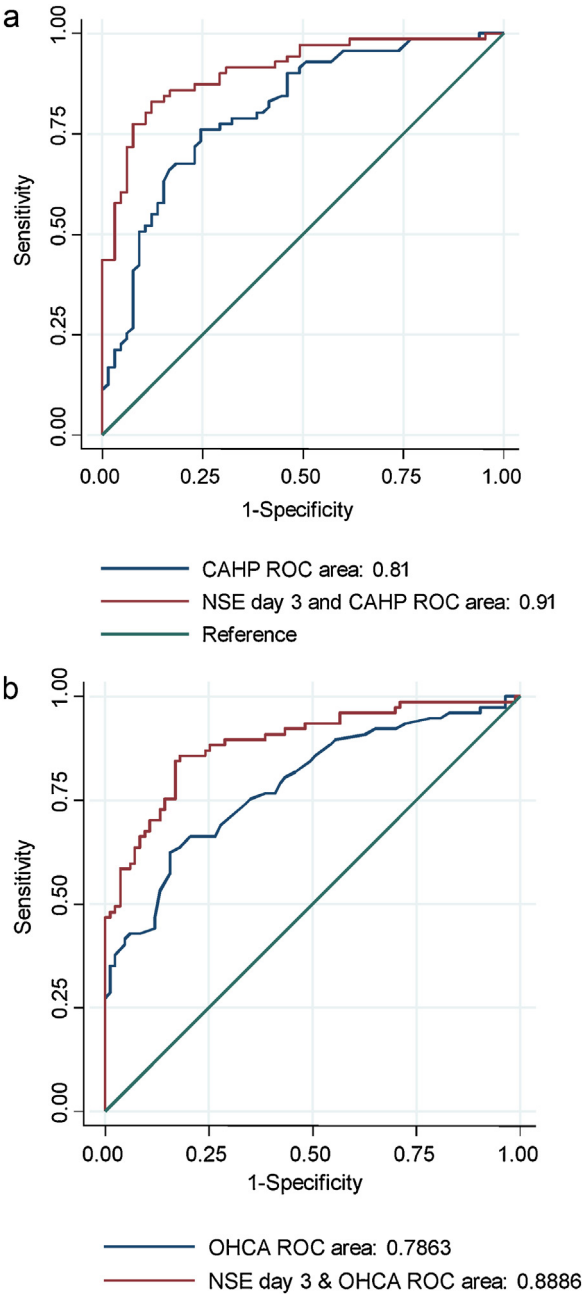

Fig. 2 – (2.1) Areas under the curve for CAHP score for endpoint neurological outcome; ROC, receiver operating characteristic. (2.2) Areas under the curve for OHCA score for endpoint neurological outcome; ROC, receiver operating characteristic. CAHP, Cardiac Arrest Hospital Prognosis; NSE, Neuron specific enolase; OHCA, Out-of-Hospital Cardiac Arrest Score.

and are thus available early in the course, but their prognostic reliability is lower compared to other clinical parameters (i.e., pupillary and corneal reactivity, motor responses and emergence of myoclonus) and ancillary electrophysiological tests including electroencephalography and somatosensory evoked potentials (SSEPs). These tests, however, provide prognostic information relatively late in the initial course of treatment, i.e. later than 72 h post-cardiac arrest.[5]

Using the available prognostic information most rationally to inform relatives about expected risks and discussing about potential withdrawal of therapy thus remains an ongoing challenge in clinical medicine. Our analysis regarding test characteristics of NSE at different time points and the combination of NSE and clincial scores may help to further improve our understanding of these prognostic tools.

The 2006 AAN guidelines recommended the NSE cutoff at 33 ng/mL for days 1 through 3,[4] and the 2015 European Resuscitation Council Guidelines for Resuscitation recommended to measure NSE 48–72 h after ROSC. In line with these recommendations, our findings indicate good PPV and NPV on days 2 and 3, but lower performance on day 1 and on admission. Also, on days 1–3, we found slightly different "optimal cutoffs" although the formerly proposed 33 ng/mL provided still fairly good information. Again, better understanding the discriminatory power of NSE for different cut-off at the different time points as shown in this study may improve use of this test in clinical practice.

An important finding of this study is the improvement in other clinical scores by addition of NSE on day 3. Cardiac arrest specific scores have been developed to risk stratify patients upon ICU admission including the OHCA and CAHP score.[15,16,27] These scores include the patient's age, initial biomarkers, and resuscitation information (i.e., pH, lactate, creatinine, no-flow time, low-flow time, cardiac arrest setting, initial rhythm). Our results indicate that combination of day 3 NSE with these scores further improve their performance and may thus have a positive impact on patient management. Future studies should in more detail compare these scores to a state of the art neurological examination to come up with an optimal set of prognostic factors and markers.

Recently, the impact of hypothermia (TMH) and targeted management (TTM) on cardiac arrest patients has been discussed. A sub-study of the TTM (Targeted Temperature Management) trial showed that there is no significant difference on NSE as an outcome predictor between patients treated at 33 °C or 36 °C.[28,29] We confirmed these results in a subgroup analysis stratifying patients treated with hypothermia (TMH) or targeted management (TTM), respectively. Another interesting finding of this study is the lower neurological outcome prediction in patients with an impella device. This may be explained by an increase in NSE-levels resulting from hemolysis caused by mechanical hemodynamic support devices. Although this finding needs further verification in other studies, physicians should be more cautious in this patient population regarding high NSE levels.

Subgroup analysis for patients suffering from epileptic seizures show higher prognostic value regarding neurological outcome, whereas there seems to be no differences concerning in-hospital mortality. Status epilepticus represents a potential confounder, as serum levels of NSE may increase during prolonged epileptic seizures or status epilepticus reflecting ictal neuronal damage,[30] and status epilepticus following hypoxic-ischemic encephalopathy is associated with unfavorable outcome after cardiac arrest.[5] We did not have detailed data regarding status epilepticus in our cohort to confirm the value of NSE in such patients.

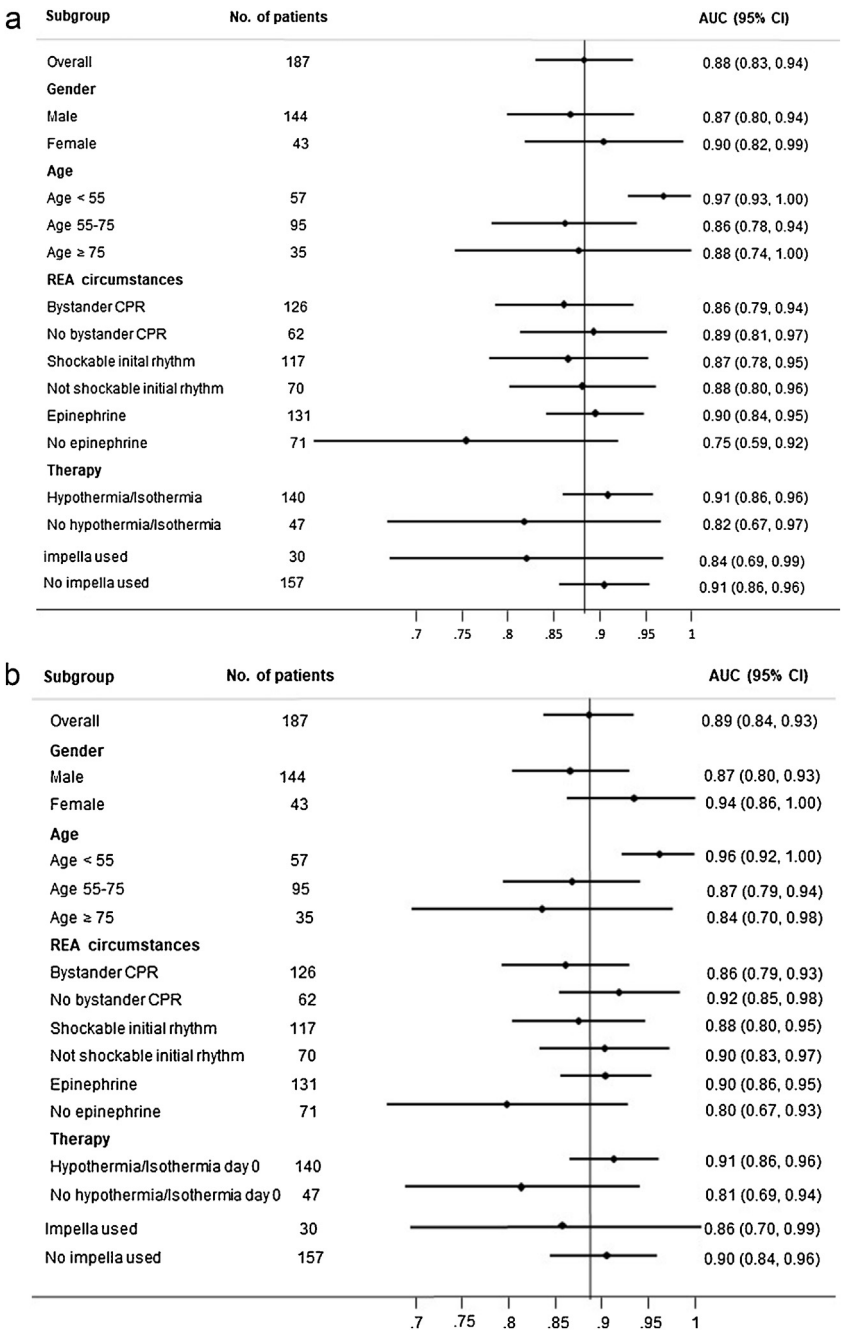

Fig. 3 – (3.1) Subgroup analysis of NSE on day 3 for endpoint neurological outcome. CPR, cardiopulmonary resuscitation; AUC, area under the curve; CI, confidence interval. (3.2) Subgroup analysis of NSE on day 3 for endpoint in-hospital death. CPR, cardiopulmonary resuscitation; AUC, area under the curve; CI, confidence interval.

Our study has several strengths and limitations. NSE was not measured on all days and only in patients residing in the ICU. We had a different number of values available at the different days due to death of patients, early discharge and missing data, which may impact the statistical analysis. We used the Roche immunoassays and fresh samples, which may correspond better to values expected in clinical routine. In a previous study using an ECLIA kit NSE values showed high variability between 15–36% between fresh or frozen samples.[31] Also, we did not collect data on neurological exams done to assess patients risk, which may also influence withdrawal of therapy. Thus, we cannot make a statement how much NSE would add to a profound neurological examination of patients. Also, we cannot in more detail look at patients with epileptic activity/status epilepticus, where NSE might increase. Also, we did not have data on hemolysis effects, transfusions/impacts on kidney (function/support or dialysis)

which could impact the results. Finally, NSE is a marker used in clinical routine and may influence decisions about withdrawal of care. However, blinding physicians was regarded impractical due to ethical considerations in our study.

Conclusions

NSE measured at day 3 significantly improves clinical risk scores for outcome prediction in cardiac arrest patients and may thus add to clinical decision making about escalation or withdrawal of therapy in this vulnerable patient population.

Conflicts of interest

None.

Funding

None of the authors has financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Ethics approval and patient consent

Our study complies with the Declaration of Helsinki. The Ethics Committee of Northwest and Central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, EKNZ) approved this study. The approval reference number is EKNZ 373/11. Either informed consent was obtained from the patient itself or, if unconscious or sedated, from a family member who served as the surrogate decision-maker. If no next of kin was readily available, a neutral treating physician not being involved in the study confirmed that there was no disapproval for inclusion from a medical point of view. In this case, patients or family members were asked to confirm their participation if possible at a later time point.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.07.003.

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